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Unravelling the Mechanisms Behind Exercise Intolerance and Recovery in Long COVID

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Running head: Mechanisms of Exercise Intolerance and Recovery in Long COVID

Abstract

Background: Patients suffering from long COVID may exhibit autonomic dysregulation. However, the association between autonomic dysregulation and exercise intolerance and the impact of therapeutic interventions on its modulation remain unclear. This study investigated the relationship between heart rate recovery at the first minute (HRR1), a proxy for autonomic imbalance, and exercise intolerance in patients with long COVID. Additionally, the study aimed to assess the effects of a 12-week home-based inspiratory muscle training program on autonomic modulation in this patient population.

Methods: This study is a post hoc subanalysis of a randomized trial in which 26 patients with long COVID were randomly assigned to receive either a 12-week inspiratory muscle training program or usual care alone (NCT05279430). The data were analyzed using Pearson's correlation and linear mixed regression analysis.

Results: The mean age was 50.4±12.2 years, and 11 (42.3%) were women. Baseline HRR1 was significantly correlated with maximal functional capacity (peakVO_2) (r=0.402, p=0.041). Patients with lower baseline HRR1 (≤ 22 bpm) exhibited higher resting heart rates and lower peakVO_2. Inspiratory muscle training led to a more substantial increase in peakVO_2 in patients with lower HRR1 at baseline (p=0.019). Additionally, a significant improvement in HRR1 was observed in the IMT group compared to the usual care group after 12-week (Δ +9.39, 95% CI=2.4-16.4, p=0.010).

Conclusion: Lower baseline HRR1 is associated with exercise intolerance in long COVID patients and may serve as a valuable criterion for identifying individuals likely to benefit more from a home-based inspiratory muscle training program.

Introduction

Long COVID syndrome is defined by the persistence or emergence of symptoms for at least four weeks following the initial SARS-CoV-2 infection [1]. The prevalence of long COVID after 6 months of acute SARS-CoV-2 infection is notably high [2], thereby triggering substantial social and economic implications. The underlying mechanisms driving this syndrome still need to be fully comprehended [1]. Cardiovascular autonomic dysregulation, often referred to as dysautonomia, is frequently observed in individuals with long COVID and has been suggested as a potential pathophysiological mechanism underlying common symptoms associated with this syndrome [3].

Cardiovascular autonomic dysregulation in long COVID is characterized by impaired vagal tone, reduced heart rate variability and a notable sympathovagal imbalance [4]. Along this line, the heart rate recovery at the first minute (HRR1) after graded exercise provides a surrogate indicator of autonomic health in individuals affected by long COVID [3], revealing the velocity of parasympathetic reactivation during the recovery phase [5,6].

Inspiratory muscle training is a physical therapy that involves targeted exercises to fortify the inspiratory musculature. Inspiratory muscle training has positively affected cardiac autonomic control in healthy individuals and across diverse chronic disease populations [7].

Even though dysautonomia is a common condition in patients affected by long COVID [3], its association with symptom severity and the impact of various therapeutic interventions on its modulation remain uncertain. The InsCOVID trial [8,9] is a randomized clinical study assessing the impact of a 12-week home-based inspiratory muscle training program on functional capacity, comparing it to standard care, within a cohort of long COVID patients who had experienced hospitalization for SARS-CoV-2 pneumonia at least 12 weeks earlier. Given these previous considerations, we hypothesized that lower values of HRR1 could help us to identify those patients

with lower exercise tolerance at baseline and higher response to a 12-week home-based inspiratory muscle training program. Therefore, in this post hoc substudy of the InsCOVID trial, we aimed to investigate the relationship between HRR1 and exercise tolerance at baseline, the effects of a 12-week inspiratory muscle training program on HRR1, and the influence of baseline HRR1 on the response to a 12-week home-based inspiratory muscle training program in a selected group of long COVID patients.

Methods

The InsCOVID trial was a single-center randomized clinical trial with blinded assessors, enrolling 26 long COVID patients. It aimed to investigate the effects of a 12-week home-based inspiratory muscle training program, compared to usual care in a 1:1 ratio, on the maximal functional capacity (peakVO_2) of individuals who had persistent symptoms (exertional dyspnea and/or fatigue) for more than 3 months following hospitalization for SARS-CoV-2 pneumonia. The trial's protocol, rationale, design, and primary outcomes were registered and previously published [8,9]. Informed consent was obtained from all participants, and the trial received approval from the local research ethics committee (Comité de Ética de la Investigación con Medicamentos del Hospital Clínic Universitari de València, 2021/226), following the principles outlined in the Declaration of Helsinki and national regulations.

Participants

The study's inclusion criteria encompassed individuals aged 18 and above previously hospitalized for SARS-CoV-2 pneumonia with ongoing symptoms for a minimum of three months and the provision of informed consent. Exclusion criteria included: (a) the inability to undergo a maximal baseline CPET; (b) the presence of structural or valve heart disease; (c) effort angina or ischemia during CPET; (d) a history of vascular or chronic obstructive pulmonary disease; (e) treatment with digitalis, calcium channel blockers, β-blockers, or ivabradine; (f) chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2); (g) individuals with pacemakers or a history of atrial fibrillation; (h) the presence of autoimmune, inflammatory, or active neoplastic diseases; (i) anemia; and (j) pregnancy.

Interventions

Patients allocated to home-based inspiratory muscle training intervention commenced with an initial diaphragmatic breathing instruction using a threshold inspiratory muscle trainer. Subsequently, patients followed a 12-week plan with two 20-minute daily sessions featuring resistance set at 25-30% of their maximal inspiratory pressure. Systematic weekly assessments conducted by a physiotherapist facilitated progressive resistance adjustments. Patients indicated good tolerance to the daily sessions.

Maximal functional capacity was evaluated using incremental and symptom-limited CPET on a bicycle ergometer, with a ramp protocol of 10 W increments every 1 min. Maximal functional capacity was defined when the patient stopped pedalling because of symptoms, and the respiratory exchange ratio was ≥1.1. PeakVO_2 was considered the highest value of oxygen consumption during the last 20 seconds of exercise, and the percent of predicted peakVO_2 was calculated using the Wasserman equation [10].

The heart rate was evaluated at rest, peak effort, and the first minute of the recovery phase. HRR1 was defined as the difference between maximal exercise heart rate and heart rate at the first minute into recovery [11].

Statistical analysis

Continuous variables were expressed as means (± standard deviation) or medians (interquartile range) and discrete as percentages. Baseline variables were compared among groups based on median baseline HRR1 values using the unpaired t-test, Wilcoxon rank sum test, or chi-square test as appropriate.

Pearson's correlation test determined correlations between HRR1 and percent of predicted peakVO_2 at baseline. A linear mixed regression model was used to analyze the effects of inspiratory muscle training program on HRR1, and the baseline value of the endpoint was included

as a covariate. We used a linear mixed regression model to analyze between-treatment changes in peakVO_2 along baseline HRR1, comparing the effects of the inspiratory muscle training intervention vs usual care. Baseline age, sex, body mass index, rest-HR, C-reactive protein, maximal inspiratory pressure, and the baseline values of peakVO_2 were included as covariates. All analyses were performed with STATA 17.0 [StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.].

Results

The mean age of the sample was 50.4±12.2 years, with 46.2% of the participants being women. Baseline characteristics across median baseline HRR1 are presented in Table 1. Overall, patients with lower HRR1 showed higher rest heart rate, lower peakVO_2, and percent of predicted peakVO_2, with no other significant differences. There were no significant differences across treatment arms (patient allocated to inspiratory muscle training program arm vs usual care arm) at baseline in the InsCOVID trial [6].

At baseline, HRR1 was moderately correlated with the percent of predicted peakVO_2 (r= 0.402, p=0.041), as shown in Figure 1. Regarding the HRR1 response to inspiratory muscle training at 12-week, a statistically significant increase in HRR1 was observed (Δ +9.39, 95% confidence interval [CI]= 2.4-16.4, p=0.010) in the inspiratory muscle training arm (Figure 2). Compared to patients in the usual care arm, individuals assigned to the inspiratory muscle training arm exhibited an enhanced increment in peakVO_2 if they presented with a lower HRR1 at baseline (p-value for between-treatment comparison=0.019), as illustrated in Figure 3.

Discussion

The main finding of this substudy of the InsCOVID trial highlights the potential role of autonomic dysfunction as a mechanistic contributor to exercise intolerance in long COVID patients. Our results revealed a significant association between baseline HRR1 and exercise tolerance or responsiveness to an inspiratory muscle training program. The present findings underscore the relevance of HRR1 as a practical, cost-effective, and easily collected surrogate for assessing autonomic nervous system function, exercise tolerance and guiding simple therapeutic interventions to improve exercise capacity in this specific patient population.

Individuals suffering from long COVID frequently present a heightened prevalence of cardiovascular autonomic dysregulation [3,4,12]. Additionally, baseline conditions of elevated body mass index and/or physical inactivity may exacerbate the impairment of autonomic modulation in long COVID patients [12]. As exercise training has demonstrated positive effects on autonomic balance in healthy individuals [6], one could anticipate analogous effects for patients grappling with long COVID. However, existing evidence that evaluated the impact of aerobic exercise and resistance training on autonomic modulation did not yield positive results [13], despite rehabilitation interventions being associated with improvements in functional exercise capacity, dyspnea, and quality of life [13,14].

Regarding inspiratory muscle training programs, previous evidence has demonstrated favourable effects on autonomic function when incorporating inspiratory muscle training into conventional rehabilitation interventions for long COVID [15]. Furthermore, in congruence with our previous findings [9], a recent meta-analysis that evaluated the effects of inspiratory muscle training in long COVID revealed significant benefits in maximal functional capacity [16].

Although the precise mechanisms by which inspiratory muscle training might improve cardiac autonomic modulation and exercise capacity remain unclear, previous literature suggests that an induced reduction in breathing frequency and increased tidal volume at rest [7], as well as potential structural changes in inspiratory muscle fibers [16,17], may be potential links between inspiratory muscle training and improvements in exercise tolerance or cardiac autonomic control. Based on previous research, HRR1 in healthy individuals is regulated by a cardiac vagal function in response to the baroreceptor and muscle reflexes [5,6]. Furthermore, prior evidence has demonstrated that decreased HRR1 is associated with poor prognosis in apparently healthy adults and those with cardiovascular diseases and systemic disorders [5]. In alignment with this idea and consistent with recent evidence, we postulate that other mechanisms could be implicated. The first is that diaphragmatic breathing and strengthening through inspiratory muscle training could modulate arterial baroreflex sensitivity, consequently improving sympathovagal balance [17]. The second is that inspiratory muscle training could attenuate the altered muscular reflexes of a highly metabolically active muscle such as the diaphragm [17,18], improving short-term exercise tolerance.

Study Limitations

Some limitations must be addressed. First, as a single-centre study, the generalizability of our results to other populations may be limited. Second, this study has a relatively small number of participants, leading to an increased risk of type II error and reduced statistical power to detect significant effects. Third, we acknowledge that this is a post-hoc analysis; the original InsCOVID study was not designed to evaluate the current hypothesis.

Conclusions

This post-hoc analysis of the InsCOVID study highlights the significance of lower baseline HRR1 values in identifying long COVID patients with diminished functional capacity in whom the incorporation of a home-based inspiratory muscle training program was associated with a greater short-term improvement in maximal functional capacity and HRR1.

These findings suggest the potential role of autonomic dysfunction as a mechanistic contributor to exercise intolerance in long COVID patients. Furthermore, inspiratory muscle training emerges as a simple and effective intervention for improving exercise tolerance in this subset of patients with long COVID and autonomic dysfunction. This hypothesis-generating analysis lays the groundwork for future prospective, well-powered, and controlled studies that assess the effects of inspiratory muscle training programs as a therapeutic in patients with long COVID and parameters of dysautonomia.

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Figure legends

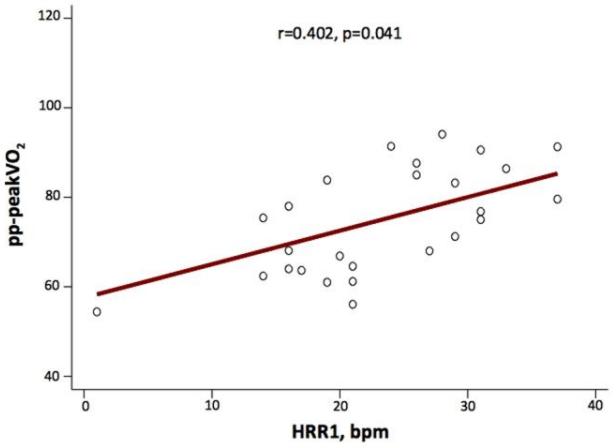

Figure 1. Correlation between HRR1 and pp-peakVO_2.

HRR1, heart rate recovery at the first minute; pp-peakVO_2, percent of predicted peak oxygen consumption.

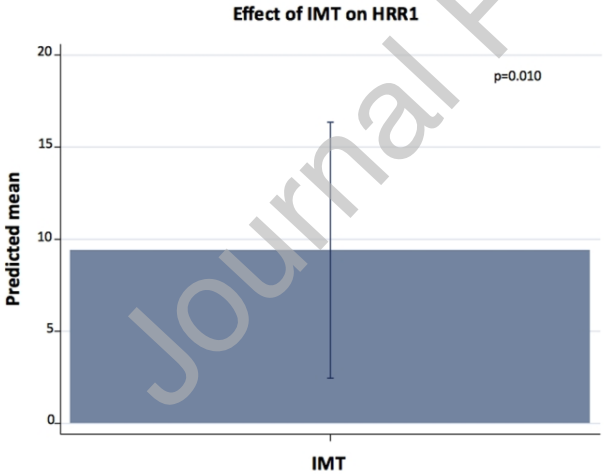

Figure 2. Change in mean HHR1 after inspiratory muscle training program compared to usual care.

HRR1, heart rate recovery at the first minute; IMT, inspiratory muscle training.

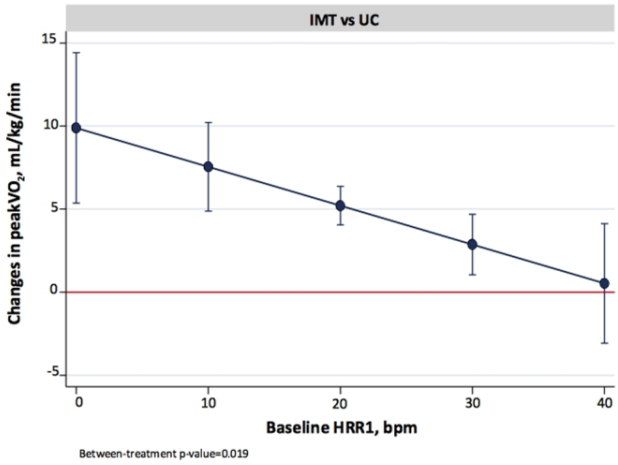

Figure 3. PeakVO2 changes across baseline HHR1.

HRR1, heart rate recovery at the first minute; IMT, inspiratory muscle training; peakVO2, peak oxygen consumption; UC, usual care.

Table 1. Baseline characteristics of the patients stratified by median baseline HRR1

Variables	All patients	HRR1 ≤ 22	HRR1 > 22	p-value
n (%)	26 (100)	13 (50)	13 (50)	
Demographic and medical history				
Age, years	50.4±12.2	49.4±13.2	51.4±11.5	0.638
Women, n (%)	11 (42.3)	4 (30.8)	7 (53.9)	0.231
BMI, kg/m^2	29 (26-32)	29 (26-31)	30 (27-32)	0.673
Hypertension, n (%)	3 (11.5)	3 (23.1)	0 (0.0)	0.033
Current smoker, n (%)	1 (3.9)	1 (7.7)	0 (0.0)	0.232
Prior smoker, n (%)	8 (30.8)	2 (15.4)	6 (46.2)	0.084
Length of hospital stay, days	8 (5-15)	9 (6-15)	7 (5-15)	0.488
Received steroids, n (%)	25 (96.2)	12 (92.3)	13 (100)	0.232
Time to the first CPET from discharge, days	362±105	360±117	365±96	0.418
Vital signs				
Heart rate at rest, b.p.m.	77±11	79±14	76±6	0.003
Systolic blood pressure at rest, mmHg	117±12	114±10	120±12	0.617

Diastolic blood pressure at rest, mmHg	61±5	62±6	61±5	0.668
Laboratory values, echocardiography parameters and pulmonary function test				
Haemoglobin, g/dL	14.6±1.1	14.8±1.2	14.3±1.1	0.792
CRP, mg/L	1.6 (0.8-3.2)	1.8 (0.8-3)	1.4 (1.1-3.9)	0.959
NT-proBNP, pg/mL	28 (14-43)	18 (11-42)	33 (18-43)	0.198
LVEF, %	65.6±6.1	67±6.9	64±5.2	0.332
PAPS, mmHg*	27.7±4.7	28±5.6	27±3.3	0.243
DLCO, %	72.5±13.3	74.3±13.5	70.6±13.3	0.960
pp-MIP, %	87 (71-103)	91 (81-103)	78 (71-93)	0.317
CPET Variables				
Workload, W	119.5±36	113±27	126±43	0.118
Exercise time, sec	684.8±218.7	648.9±162.1	720±265.7	0.100
Peak heart rate, bpm	139±20	139±24	140±17	0.218
Chronotropic index†	0.64±0.19	0.66±0.20	0.70±0.19	0.881
Peak systolic blood pressure, mmHg	157±20	154±19	159±21	0.710
RER	1.12 (1.1-1.16)	1.11 (1.1-1.16)	1.12 (1.1-1.13)	0.872

PeakVO_2, mL/kg/min	18.9±5	18.2±3.1	19.6±6.4	0.018
Percent of predicted peakVO_2, %	75.2 (62.4-86.4)	63.5 (61-68.1)	85 (77-90.6)	0.009
VE/VCO_2 slope	29.4±5.2	29.5±6	29.2±4.4	0.279

*Data available in 15 patients (9 in the HRR1 ≤ 22 group and 6 in the HRR1 > 22 group).

†Cronotropic index formula= peak HR-rest HR/ [(220-age)-restHR)].

Continuous variables are presented as median (interquartile range), and categorical variables are as percentages.

BMI, body mass index; CPET, cardiopulmonary exercise testing; CRP, C-reactive protein; DLCO, diffusing capacity of the lungs for carbon monoxide; LVEF: left ventricle ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide; PASP: pulmonary artery systolic pressure; peakVO_2, peak oxygen consumption; pp-MIP, percent of predicted maximal inspiratory pressure; pp-peakVO_2, percent of predicted peak oxygen consumption, RER, respiratory exchange ratio; VE/VCO_2slope, ventilatory efficiency.

Clinical Significance:

• The heart rate recovery at the first minute (HRR1), a surrogate of autonomic function, was associated with exercise intolerance in long COVID.

• Lower HRR1 at baseline identifies those patients with poor exercise tolerance and those likely to benefit more from a home-based inspiratory muscle training program.

• Home-based inspiratory muscle training program significantly increased exercise tolerance in patients with long COVID, especially those with baseline dysautonomia.